REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-10 are pending.

The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. Support for amended claim 1 may be found, inter alia, at page 4, line 16, of the specification. Basis for amended claim 4 and new claim 10 may be found, inter alia, at page 5, lines 19-21 and lines 27-28, respectively, of the specification.

Claim 1 was objected to as allegedly informal. It is corrected as suggested by the Examiner. Withdrawal of the objection is requested.

35 U.S.C. 112 – Definiteness

Claims 1 and 4 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

Claim 1 is amended to clarify that R^3 is not present in formula 2.

Claim 4 is amended to clarify the chemistry of the "chemically and configurationally stable derivative" as described in one embodiment at page 5, lines 19-21, of the specification. Claim 10 is directed to another embodiment. But one of skill in the art would recognize that other chemically and configurationally stable derivatives are within the scope of transformed products of the amino aldehyde or a salt thereof according to claim 1.

Applicants request withdrawal of the Section 112, second paragraph, rejections because the pending claims are clear and definite.

35 U.S.C. 103 – Nonobviousness

To establish a case of prima facie obviousness, all of the claim limitations must be taught or suggested by the prior art. See M.P.E.P. § 2143.03. Obviousness can only be established by combining or modifying the prior art teachings to produce the claimed invention if there is some teaching, suggestion, or motivation to do so found in either the

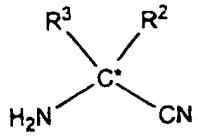
references themselves or in the knowledge generally available to a person of ordinary skill in the art. See, e.g., *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941, 1943-44 (Fed. Cir. 1992). Evidence of the teaching, suggestion or motivation to combine or to modify references may come explicitly from statements in the prior art, the knowledge of a person of ordinary skill in the art or the nature of the problem to be solved, or may be implicit from the prior art as a whole rather than expressly stated in a reference. See *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999); *In re Kotzab*, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000). Rigorous application of this requirement is the best defense against the subtle, but powerful, attraction of an obviousness analysis based on hindsight. See *Dembiczak* at 1617. Whether shown explicitly or implicitly, however, broad conclusory statements standing alone are not evidence because the showing must be clear and particular. See *id.*

Thus, it is well established that the mere fact that references can be combined does not render the resultant combination obvious unless the desirability of that combination is also taught or suggested by the prior art. See *In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990). Therefore, even if all elements of the claimed invention were known, this is not sufficient by itself to establish a prima facie case of obviousness without some evidence that one would have been motivated to combine those teachings as proposed by the Examiner. See *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (B.P.A.I. 1993). Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1-3 and 5-9 were rejected under Section 103(a) as allegedly unpatentable over Umio (Yakugaku Zasshi - J. Pharm. Soc. Japan 78:1072-1074, 1958). Applicants traverse.

It was asserted at page 4 of the Action that "one of ordinary skill would have immediately recognized that no reaction (and therefore no racemization) would take place at any asymmetric carbon adjacent to the nitrile being reduced." No evidence or reasoning from the evidence of record was cited in the Action for this allegation and, therefore it is respectfully requested that if this rejection is maintained, the basis for the Examiner's statement be provided in a non-final Action so Applicants can respond.

In contradiction to allegations made in the Action, one of ordinary skill in the art at the time that Applicants' invention was made would have expected racemization to occur because the general belief was that for α-amino nitriles of the claimed process:

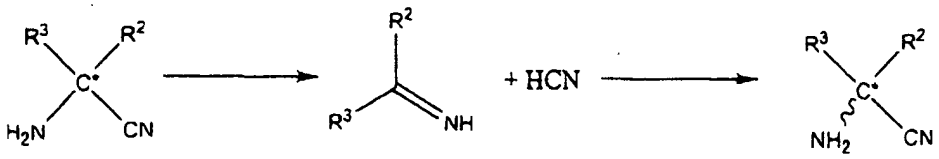


racemization would occur under protic conditions (e.g., in H_2O or H_2O/methanol). See the discussion of literature below. In other words, a prejudice against using enantiomerically enriched α-amino nitriles to prepare another enantiomerically enriched compound existed, because one of ordinary skill in the art would have expected racemization of the enantiomerically enriched α-amino nitrile and, hence, a low enantiomeric excess of the compound produced therefrom.

Specifically, one of ordinary skill in the art would not have considered it to be possible to prepare enantiomerically enriched alcohols or aldehydes from the corresponding enantiomerically enriched α-amino nitriles under protic conditions like "in the presence of an aqueous solvent" as it would have been expected that α-amino nitriles would racemize.

Racemization mechanism of the α-amino nitrile:

It is likely that a retro Strecker reaction occurs on the α-amino nitrile (disassociation of the molecule). If the molecule would then again be synthesized via the Strecker reaction, the other enantiomer could be formed; hence racemizing the α-amino nitrile. This is shown below:



Furthermore, the literature provided additional evidence that one of ordinary skill in the art would have expected that under protic conditions, enantiomerically enriched

amino alcohols or amino aldehydes cannot be prepared from enantiomerically enriched α-amino nitriles.

Japan Energy Corp. (see attached JP 5286919 and English-language abstract) discloses the production of racemic amino nitriles from optically active amino nitriles using a cyanide salt in a protic solvent (e.g., lower alcohol(s) or a mixture of benzene/ methanol).

Gastrock et al. (already of record as U.S. Patent 4,683,324 on the Form PTO-1449) disclose racemization of amino nitriles (I) under protic conditions (see col. 2, lines 53-56). Also see col. 2, lines 35-39; col. 2, lines 53-56 (protic solvents); col. 2, line 67, to col. 3, line 4.

American Cyanamid (see attached EP 1 050 529 A2) discloses at [0002] that (R) amino butyronitrile is an unstable compound that readily racemizes upon standing. The solution taught is to use a substantially water-free non-polar solvent [0005]. Hence, this document teaches away from the use of an aqueous (protic) solvent.

Therefore, it was surprising at the time the invention was made that an enantiomerically enriched compound could be prepared easily in high yields starting from enantiomerically enriched α-amino nitriles without substantial racemization (see page 2, lines 27-29, of the specification) in accordance with the claimed process. This can also be seen from the Examples 11-17 of Applicants' specification, where it is shown that the enantiomeric excess of the starting compound is largely retained in the end-product.

In other words, one of ordinary skill in the art facing the problem of finding a commercially attractive route for the production of (N-protected) amino alcohols or of amino aldehydes would not have considered a process starting from enantiomerically enriched α-amino nitriles, since it would have been expected that racemization of α-amino nitriles would occur (as evidenced by the literature cited above) and hence the desired compounds would not have been obtained with (high) enantiomeric excess.

Claims 1-9 were rejected under Section 103(a) as allegedly unpatentable over Perez et al. (Anal. Quim. Ser. C. 82:11-17, 1986). Applicants traverse.

The Examiner's interpretation of this Spanish-language document is incorrect. In Perez et al., as well as in its English-language abstract, amino nitrile synthesis is

described as giving epimeric mixtures, which means mixtures of stereoisomers that differ from each other in their atomic arrangement in space. All of the original galactose or glucose centers remain the same, but the amino nitrile center (i.e., carbon adjacent to the nitrile) is a mixture ("mezclas" in Spanish) of enantiomers.

This fact is made clear in the "RESULTADOS Y DISCUSION" section where it states that the treatment of *N*-ethyl or *N*-isopropyl p-D-galactopyranosylamine with HCN in methanol gave mixtures of epimers of nitriles, and the mixtures could not be separated from each other. These epimeric mixtures of nitriles upon hydrogenation again gave mixtures of epimers of amino sugars (i.e., amino aldehydes in glucopyranose form).

As can be seen from the structure shown at the top of the left-hand column on page 12, the C-atom adjacent to the nitrile has two structural configurations (1 + 2 or 3 + 4), making clear that the C-atom has two configurations in the mixture. Hydrogenation also gives mixtures of two configurations at the same C-atom (see the sentence below the structures). Or in a reaction scheme: 1 + 2 → 9 + 10 or 3 + 4 → 11 + 12.

Moreover, it is also made clear for the structures 5 + 6 or 7 + 8 that mixtures of 16 + 17 or 18 + 19, respectively, are obtained upon hydrogenation (first paragraph of right-hand column on page 12). As can be seen from the structure shown in the middle of the right-hand column on page 12, again there are two configurations for the carbon with the R^1 and R^2 groups as substituent (i.e., carbon adjacent to the nitrile).

Therefore, the correct interpretation of the cited document is that hydrogenation of a mixture of enantiomers (i.e., enantiomers with respect to the asymmetric C adjacent to the nitrile) gives a product, which is a mixture of enantiomers as well.

Perez et al. do not teach that racemization does not occur. Racemization might still occur because there is no indication of the enantiomeric excess in the mixtures, or that they may even be racemic mixtures. Therefore, Perez et al. would neither teach nor suggest to one of ordinary skill in the art that hydrogenation of an enantiomerically enriched nitrile will give an enantiomerically enriched alcohol or aldehyde product. In other words, there is no teaching or suggestion in Perez et al. that the stereochemistry

of the asymmetric carbon adjacent to the nitrile in the starting material is preserved in the product.

Withdrawal of the Section 103 rejections is requested because the invention as claimed would not have been obvious to one of ordinary skill in the art at the time it was made.

Conclusion

Having fully responded to all of the pending objections and rejections contained in this Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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(54) Aminobutyronitrile compositions

(57) There is provided a stable optically active composition comprising up to about 65% by weight of (R)2-amino-2,3-dimethylbutyronitrile and a substantially water-free non-polar solvent. Said composition is useful in the manufacture of agriculturally active agents.

EP 1 050 529 A2

Description

BACKGROUND OF THE INVENTION

[0001] Phenoxypropionic acid cyanimide derivatives, such as those described in EP 262,393 and Research Disclosure 92306005, are useful as fungicides, particularly for the control of the causative agents of rice blast. Said cyanimide derivatives contain assymetric or stereogenic carbon atoms and it has been demonstrated that those derivatives having the R-configuration show enhanced fungicidal activity over that of the corresponding racemic mixtures. Similarly, the imidazolinone family of herbicides, such as those described in U.S. 4,798,619 and U.S. 5,334,576, contain assymetric or stereogenic carbon atoms and it has been demonstrated that those imidazolinones having the R-configuration on the dialkylsubstituted carbon atom in the imidazolinone ring show a greater herbicidal activity than the corresponding racemic mixtures.

[0002] A common key chiral intermediate compound, (R)2-amino-2,3-butyronitrile may be used to prepare the above-said agriculturally active compounds. However, said (R)aminobutyronitrile compound is unstable and readily racemizes upon standing, thus making practical manufacturing procedures difficult.

[0003] Therefore, it is an object of this invention to provide a stable (R)2-amino-2,3-dimethylbutyronitrile composition useful for the manufacture of agriculturally active compounds.

[0004] It is another object of this invention to provide a readily available, storage-stable source of (R)2-amino-2,3-dimethylbutyronitrile.

SUMMARY OF THE INVENTION

[0005] The present invention provides a stable chiral composition which comprises up to about 65% by weight of (R)2-amino-2,3-dimethylbutyronitrile and a substantially water-free non-polar solvent. Said compositions are useful as intermediates in the manufacture of agriculturally active agents such as fungicidal cyanimides and herbicidal imidazolinones having the R-configuration.

DETAILED DESCRIPTION OF THE INVENTION

[0006] Fungicidal α-phenoxypropionic acid cyanimide derivatives and their preparation from (R)2-amino-2,3-dimethylbutyronitrile are described in Research Disclosure 92306005. Herbicidal imidazolinones and their preparation from (R)2-amino-2,3-dimethylbutyronitrile are described in U.S. 4,683,324. Said patent also describes the preparation and isolation of (R)2-amino-2,3-dimethylbutyronitrile. Although said (R)aminobutyronitrile may be potentially useful as a key common intermediate in the manufacture of agriculturally active agents such as fungicides and herbicides, its half-life is estimated to be less than 8 hours at room temperature, therefore, making its use in a manufacturing procedure highly impractical.

[0007] Surprisingly, it has now been found that a composition which comprises up to about 65%, preferably 5% to 65%, more preferably 5% to 50%, especially preferably 15% to 40%, by weight of (R)2-amino-2,3-dimethylbutyronitrile (hereinafter designated R-aminonitrile) and a substantially water-free non-polar solvent is storage-stable for prolonged periods of time at temperatures at or below room temperature (up to about 25°C). Higher temperatures or higher concentrations may be employed, in the inventive compositions, however higher temperatures or higher concentrations accelerate the racemization process while lower temperatures or lower concentrations decrease the rate of racemization and increase the storage-stable period of time.

[0008] Advantageously, the composition of the invention may be employed in a practical manufacturing procedure, such as a process to prepare fungicidal α-phenoxycyanimides or herbicidal imidazolinones having the R configuration, without rapid decomposition due to racemization of or loss of HCN from, the R-aminonitrile starting material. Further, the stability of the composition of the invention allows for interim storage or transportation of the R-aminonitrile compound as needed for manufacturing purposes. It is intended that the stable chiral aminobutyronitrile compositions of the invention also embrace the corresponding essentially enantiomerically pure (S)2-amino-2,3-dimethylbutyronitrile compound as the chiral component therein.

[0009] Non-polar solvents useful in the composition of the invention are aromatic hydrocarbons (e.g. toluene, benzene, xylene, naphthalene and the like preferably toluene), halogenated aromatic hydrocarbons (e.g. chlorobenzene, dichlorobenzenes and the like), hydrocarbons (e.g. pentanes, hexanes and the like), halogenated hydrocarbons (e.g. chloroform, methylene chloride, dichloroethane, and the like, esters (e.g. ethyl acetate, methyl propionate and the like), ethers (e.g. diethyl ether, tetrahydrofuran, dioxane and the like) or any of the conventional, preferably water immiscible, organic non-polar solvents.

[0010] Preferred non-polar solvents suitable for the composition of the invention are aromatic hydrocarbons, particularly toluene.

[0011] In order to facilitate a further understanding of the invention, the following examples are presented primarily for the purpose of illustrating certain more specific details thereof. The invention is not to be deemed limited thereby except as defined in the claims.

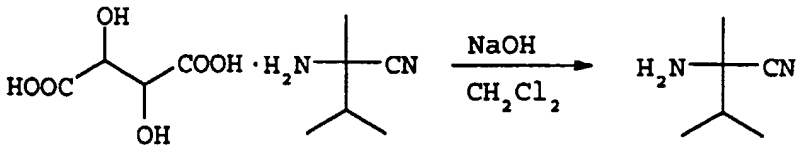
[0012] Unless otherwise noted, all parts are parts by weight. HPLC designates high performance liquid chromatography.

EXAMPLE 1

Evaluation Of The Solvent Effect On The Racemization Of A 10% Solution of (R)2-Amino-2,3-dimethylbutyronitrile

A) Preparation of (R)2-Amino-2,3-dimethylbutyronitrile

[0013]



(2S,3S) (R) (R)

[0014] A mixture of methylene chloride, ice, (R)2-amino-2,3-dimethylbutyronitrile (2S,3S) tartaric acid salt (8.13g, 31.0 mmol) and 50% NaOH (5.3 ml, 8.0 g, 100 mmol NaOH) is shaken until no solid particles are observed. The organic phase is separated, dried over $MgSO_4$ and filtered. The filtrate is distilled *in vacuo* at 20°C to remove the methylene chloride and obtain free (R)2-amino-2,3-dimethylbutyronirile as a clear liquid, 3.42 g (98.3% yield).

B) Optical Rotation Evaluation

[0015] In these evaluations, 10% wt/wt solutions of the freshly prepared (R)2-amino-2,3-dimethylbutyronitrile in a variety of solvents are placed in a constant temperature bath. Optical rotations, ($[\alpha]_D$) are determined at time 0 and at regular intervals thereafter. The data obtained are shown in Tables I and II.

Table I

Evaluation of Non-polar Solvent Effect On Stability Of (R)2-Amino,2,3-dimethylbutronitrile Compositions

Solvent	Time (Hr.)	$[\alpha]_D$	$\Delta^1[\alpha]_D$	Temperature (°C)
Ethyl Acetate	0	-00.422		26
	1	-00.422		26
	2.5	-00.425		26
	3.5	-00.424	-0.002	26
	4.5	-00.424		26
	19.5	-00.421		26
		-00.423		26
Toluene	0	-00.423		26
	1	-00.423		26
	2	-00.423		26
	7	-00.423	0.000	26
	23	-00.423		26
Acetonitrile	0	-00.209		26
	1	-00.204		26
	2	-00.199		26
	3	-00.197	0.012	26
	312	-00.025		26

Solvent	Time (Hr.)	$[\alpha]_D$	$\Delta^1[\alpha]_D$	Temperature (°C)
Tetrahydrofuran	0	-00.520		26
	1	-00.520		26
	2	-00.518		26
	4.5	-00.518	0.002	26
	27	-00.515		26
Methylene Chloride	0	-00.468		26
	1	-00.467		26
	2	-00.461	0.007	26
	17.5	-00.458		26
Chloroform	0	-00.547		26
	1	-00.549		26
	2	-00.547	0.000	26
	17.5	-00.540		26
Dimethyl Formamide	0	-00.081		26
	1	-00.074		26
	3	-00.062	0.019	26
	23	-00.015		26
	168	+00.002		26

Solvent	Time (Hr.)	$[\alpha]_D$	$\Delta'[\alpha]_D$	Temperature (°C)
Ethyl Ether	0	-00.505		26
	1	-00.505		26
	4	-00.502	0.003	26
	6	-00.504		26
Hexanes	0	-00.492		26
	1	-00.494		26
	4	-00.491	0.001	26
	6	-00.482		26
Chlorobenzene	0	-00.306		25
	1	-00.304		25
	3	-00.289	0.017	25
	20.5	-00.285		25
o-Dichlorobenzene	0	-00.242		25
	1	-00.241		25
	3	-00.240	0.002	25
	20.5	-00.229		25
Nitrobenzene	0	-00.068		25
	1	-00.051		25
	3	-00.045	0.023	25
	20.5	-00.053		25

Solvent	Time (Hr.)	$[\alpha]_D$	$\Delta^1[\alpha]_D$	Temperature (°C)
1,2-Dichloroethane	0	-00.419		25
	2	-00.408		25
	4	-00.421	-0.002	25
	6	-00.436		25
1,2-Dimethoxyethane	0	-00.493		25
	2	-00.494		25
	4	-00.508	-0.015	25
	6	-00.514		25
2-Butanone	0	-00.368		25
	2	-00.366		25
	4	-00.358	0.014	25
	6	-00.357		25
Xylenes	0	-00.447		25
	2	-00.442		25
	4	-00.453	-0.006	25
	6	-00.460		25

[1] $\Delta [\alpha]_D = [\alpha]_D$ at Time 0 minus $[\alpha]_D$ at Time T

Table II

Comparative Evaluation of Polar Solvent Effect On Stability Of (R)2-Amino,2,3-dimethylbutronitrile Compositions				
Solvent	**Time (Hr.)**	**$[\alpha]_D$**	**$\Delta^1 [\alpha]_D$**	**Temperature (°C)**
Methanol	0	-00.500		26
	1	-00.173		27
	2	-00.054		27
	3	-00.015	0.485	26
(±)2-Butanol	0	-00.541		26
	1	-00.425		26
	2	-00.359		26
	4.5	-00.230	0.311	26
	27	-00.000		26
Dimethylsulfoxide	0	-00.239		26
	1	-00.151		26
	3	-00.059	0.180	26
	23	+00.003		26
	168	-00.003		26
Ethanol	0	-00.540		26
	1	-00.298		26
	2	-00.145		26
	4	-00.064	0.476	26
	6	-00.022		

[1] $\Delta [\alpha]_D = [\alpha]_D$ at Time 0 minus $[\alpha]_D$ at Time T

As can be seen from the data shown in Tables I and II above, racemization is decreased by a factor of 10 to 100 fold when the chiral compound is present as a 10% solution in a non-polar solvent as compared to when it is present as a 10% solution in a polar solvent.

EXAMPLE 2

Comparative Evaluation Of The Effect Of Water On The Racemization Of A Toluene Solution Of (R)2-Amino-2,3-dimethylbutyronitrile

[0016] In this evaluation, (R)2-amino-2,3-dimethylbutyronitrile is prepared in a manner similar to that described in part A of Example 1 and employing toluene in place of methylene chloride. Upon extraction and separation, a 25.8% solution of free 2-amino-2,3-dimethylbutyronitrile in toluene is obtained. Immediately after extraction, the % R isomer of the water wet toluene solution is determined by HPLC analysis. The wet solution is stored at 25°C for 24 hours and a second measurement is taken. The wet solution is then dried azeotropically (45°-50°C/60-65 mmHg), analyzed for % R isomer by chiral HPLC immediately after drying, stored at 25°C for 4 days and analyzed a second time. The results are shown in Table III.

Table III

Comparative Evaluation Of The Effect Of Water On The Stability Of (R)2-Amino,2,3-dimethylbutronitrile Compositions			
Solvent	**Time (Days)**	**% R Isomer**	**Δ% R[1]**
Wet Toluene (comparison)	0	85.2	
Wet Toluene (comparison	1	80.3	-4.9
Dry Toluene (invention)	0	79.5	
Dry Toluene (invention)	4	78.9	-0.6

[1] Δ%R = % R at Time 0 minus % R at Time T

As can be seen from the data in Table III above, solutions of the chiral compound in essentially the absence of water are significantly more stable than those solutions in which water is present.

EXAMPLE 3

Evaluation Of The Effect Of Temperature And Concentration On The Racemization Of A Solution of (R)2-Amino-2,3-dimethylbutyronitrile

[0017] In these evaluations, the test solution is prepared in essentially the same manner as described in Example 2 and the solution is azeotropically dried immediately following extraction. A 50 g sample of the thus-prepared test solution is introduced into a 3-necked round bottom flask which has been set at a predetermined temperature and flushed with nitrogen. Samples of the test solution are taken directly from the flask at 0, 4, 24 and 48 hour intervals and analyzed for % R isomer and wt % concentration of (R,S)2-amino-2,3-dimethylbutyronitrile by chiral HPLC. The data obtained are shown in Table IV.

Table IV

Evaluation of The Effect Of Concentration And Temperature On the Stability Of (R)2-Amino,2,3-dimethylbutyronitrile Compositions				
Concentration (wt %)	Temperature (°C)	Time (Hr.)	%R Isomer	Δ% R[1]
19.2	15	0	94.0	
19.5	15	4	93.9	
19.4	15	24	93.9	
19.2	15	48	93.6	0.4
19.2	20	0	94.2	
19.2	20	24	94.0	
19.2	20	48	94.0	0.2
19.2	60	0	94.0	
19.5	60	4	91.9	
19.8	60	24	81.6	
20.2	60	48	71.6	22.4
32.2	20	0	93.5	
32.2	20	48	93.1	0.4
38.6	2	0	93.4	
37.2	2	144	92.9	0.5
38.7	2	336	91.7	
38.6	35	0	93.4	
39.0	35	24	86.9	
38.1	35	48	84.1	9.3
38.3	20	0	90.5	
38.3	20	24	89.5	

[1] Δ%R = %R at Time 0 minus %R at 48 hr.

Table IV

Concentration (wt %)	Temperature (°C)	Time (Hr.)	%R Isomer	Δ% R[1]
37.2	35	0	92.9	
36.8	35	4	91.4	
36.8	35	24	88.4	
39.2	35	48	84.3	8.6
45.9	45	0	94.4	
46.5	47	2	89.4	
65.2	15	0	92.8	
63.8	15	4	92.6	
64.9	15	24	90.8	
63.4	15	48	89.9	2.9
65.2	60	0	92.8	
64.4	60	4	71.3	
63.4	60	24	51.4	
66.0	60	48	50.5	42.4

[1] Δ%R = %R at Time 0 minus %R at 48 hr.

As can be seen from the data shown in Table IV above, high concentration combined with high temperature decreases the stability of the chiral solution, however concentrations as high as 65% may be stable at moderate temperature.

Claims

1. A stable composition which comprises up to about 65% by weight of (R)2-amino-2,3-dimethylbutyronitrile and a substantially water-free non-polar solvent.

2. The composition according to claim 1 wherein the (R)2-amino-2,3-dimethylbutyronitrile is present at about 5% to 65% by weight.

3. The composition according to claim 1 wherein the (R)2-amino-2,3-dimethylbutyronitrile is present at about 5% to 50% by weight.

4. The composition according to claim 1 wherein the solvent is selected from the group consisting of aromatic hydrocarbons, halogenated aromatic hydrocarbons, hydrocarbons, halogenated hydrocarbons, esters and ethers.

5. The composition according to claim 4 wherein the solvent is an aromatic hydrocarbon.

6. The composition according to claim 5 wherein the solvent is toluene.

7. The composition according to claim 6 wherein the (R)2-amino-2,3-dimethylbutyronitrile is present at about 5% to 65% by weight.

8. The composition according to claim 7 wherein the (R)2-amino-2,3-dimethytbutyronitrile is present at about 15% to 40% by weight.

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M2 - [01] D010 D011 D020 D040 D601 F010 F014 F020 F521 G001 G010 G011 G012 G013 G100 H1 H100 H101 H181 H182 H401 H441 H481 H598 K0 K224 L1 L145 L250 M210 M211 M271 M280 M281 M311 M312 M313 M314 M315 M316 M321 M331 M332 M333 M340 M342 M343 M344 M349 M371 M381 M383 M391 M412 M413 M414 M416 M510 M511 M520 M521 M530 M531 M540 M620 M720 M800 M903 M904 N104 N171 N512 N513; 9348-21701-P
M3 - [01] D010 D011 D020 D040 D601 F010 F014 F020 F521 G001 G010 G011 G012 G013 G100 H1 H100 H101 H181 H182 H401 H441 H481 H598 K0 K224 L1 L145 L250 M210 M211 M271 M280 M281 M311 M312 M313 M314 M315 M316 M321 M331 M332 M333 M340 M342 M343 M344 M349 M371 M381 M383 M391 M412 M413 M414 M416 M510 M511 M520 M521 M530 M531 M540 M620 M720 M800 M903 M904 N104 N171 N512 N513; 9348-21701-P
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AB - J05286919 Prepn. of racemic 2-aminonitrile(s) (I) comprises racemisaton of optically active 2-aminonitrile(s) (II) by treating (II) with cyanic acid cpd(s). (III) in organic solvent.
- ADVANTAGE - (II) is converted to (I) under mild conditions quite efficiently in a short time; for example, D-(II) is converted to (I) from which L-(II) is isolated. Starting material (II) is prepd. from aldehyde by Strecker reaction. (IIa) or (IIb) and (III) (pref. Li cyanide, Na cyanide, K cyanide) are dissolved in solvent, pref. lower alcohol(s) or a mixt. of benzene/methanol = 85/15, the soln. is held to 20-50 deg.C for 10-60 minutes to obtain (I) soln. and (I) isolated from the soln. In the formulae R is opt. substd. alkyl, phenyl, imidazolyl, indolyl, furyl, pyridyl, thiazolyl.
- Example: Racemization of D-2-amino-2-phenylethanenitrile (IIc). (IIc) (50 mg), potassium cyanide (5 mg) were dissolved in methanol (5 ml), the solution was stirred at 40 deg.C for 10 min. The resulting matter was concentrated, the residue was recrystallized from benzene/hexane mixture to obtain racemic 2-amino-2-phenylethanenitrile. Conversion of (IIc) was 100%. On the other hand, (IIc) was treated similarly in absence of potassium cyanide, conversion of (IIc) was 57%.
- (Dwg.0/0)
CN - 9348-21701-P
IW - IMPROVE RACEMIC AMINO NITRILE PREPN

NITRILE POTASSIUM CYANIDE BENZENE METHANOL MIXTURE

IKW - IMPROVE RACEMIC AMINO NITRILE COMPRISE CONTACT OPTICAL ACTIVE AMINO NITRILE POTASSIUM CYANIDE BENZENE METHANOL MIXTURE

NC - 001

OPD - 1992-04-08

ORD - 1993-11-02

PAW - (NIHA) NIKKO KYOSEKI KK

TI - Improved racemisation for 2-amino:nitrile(s) - comprises contacting optically active 2-amino:nitrile(s) with potassium cyanide in benzene-methanol mixt.

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(54)【発明の名称】　２－アミノニトリルラセミ体の製造法

(57)【要約】

【構成】　光学活性な２－アミノニトリルを、有機溶媒中で青酸化合物と作用させて光学活性な２－アミノニトリルをラセミ体に変換し、これを取得することよりなる２－アミノニトリルラセミ体の製造法。

【効果】　光学活性な２－アミノニトリルを温和な条件で効率よくラセミ化することができる。得られたラセミ体は、光学活性α－アミノ酸の製造原料として有用である。

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【特許請求の範囲】

【請求項1】　光学活性な2－アミノニトリルを、有機溶媒中で青酸化合物と作用させて光学活性2－アミノニトリルをラセミ体に変換し、これを取得することを特徴とする2－アミノニトリルラセミ体の製造法。

【発明の詳細な説明】

【0001】

【産業上の利用分野】本発明は、光学活性な2－アミノニトリルを青酸化合物の作用によりラセミ化しラセミ体の2－アミノニトリルを製造する方法に関する。

【0002】

【従来の技術】合成法による光学活性α－アミノ酸の製造では、ストレッカー法或はその変法を用いてラセミ化α－アミノ酸を合成し、ついで当該アミノ酸を光学分割して光学活性α－アミノ酸を製造している。そして、ストレッカー法によるα－アミノ酸合成における合成中間体のラセミ化2－アミノニトリルから微生物を利用して光学活性なα－アミノ酸を製造しようとする試みがこれまで多数報告されてきた〔文献1：Y. Fukuda, et al., J. Ferment, Technol., 49, 1011(1971);文献2：特表昭63-500004 号公報；文献3：J. C. Jallageas et al., Adv. Biochem.Engineer., 14, 1(1980)〕。これらの文献に記載されている方法は原理的にはニトリル加水分解酵素による速度論的光学分割であるが、文献には、残存する光学活性な2－アミノニトリルのラセミ化の工程が含まれておらず、引き続きこの光学活性な2－アミノニトリルが加水分解されているので結局生成するのはラセミ体（文献1）あるいは光学純度の低いアミノ酸（文献2）であったり、あるいはL体のアミノ酸とD体のアミノ酸アミドとの混合物（文献3）である。本発明のラセミ化工程をこれらの方法に加えることにより、ニトリル加水分解酵素により、水解されずに残存する光学活性な2－アミノニトリルをラセミ化し、次いでこれを不斉水解するようにできるため、この工程を繰り返すことにより高光学純度の光学活性なアミノ酸を収率良く合成することができる。

【0003】2－アミノニトリルのラセミ化方法は、酒石酸類による光学分割の際にラセミ化を同時に行う方法（USP4,683,324、特開昭48-13341号公報、特開昭53-71021号公報、特開昭54-48729号公報）が知られており、ケトン、アルデヒドを添加すると反応速度および収率が向上することが記載されている。しかしながら、ラセミ化の速度は極めて遅く、また、ラセミ化だけを行う方法は知られていない。

【0004】

【発明が解決しようとする課題】本発明は光学活性な2－アミノニトリルを温和な条件で効率よくラセミ化する方法を提供することを目的とする。またさらに、本発明は、高光学純度の光学活性アミノ酸製造の原料となる2－アミノニトリルラセミ体を収率よく得ることを目的とする。

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【0005】

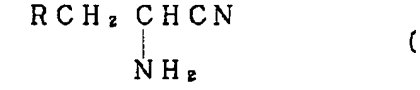
【課題を解決するための手段】本発明者らは、上記課題を達成するために鋭意検討した結果、青酸化合物を有機溶媒中で光学活性な2－アミノニトリル化合物と作用させると、光学活性な2－アミノニトリル化合物が、容易にラセミ化することを見出した。本発明は、かかる知見に基づいてなされたものである。すなわち、本発明は、次の一般式（1）及び（2）で示される光学活性な2－アミノニトリルを有機溶媒中で青酸化合物と作用させて光学活性な2－アミノニトリルを一般式に相当するラセミ体のα－ニトリル化合物に変換し、これを取得することよりなる2－アミノニトリルラセミ体の製造法である。

【0006】

【化1】

（1）

【化2】



（2）

（ただし、式中、Rはアルキル基、置換アルキル基、フェニル基、置換フェニル基、イミダゾリル基、置換イミダゾリル基、インドリル基、置換インドリル基、フリル基、置換フリル基、ピリジル基、置換ピリジル基、チアゾリル基、置換チアゾリル基を示す）。

【0007】本発明におけるニトリル化合物としては、2－アミノプロパンニトリル、2－アミノブタンニトリル、2－アミノ－3－メチルブタンニトリル、2－アミノ－4－メチルペンタンニトリル、2－アミノ－3－メチルペンタンニトリル、2－アミノ－3－ヒドロキシプロパンニトリル、2－アミノ－3－ヒドロキシブタンニトリル、2－アミノ－5－グアニジノペンタンニトリル、2－アミノ－3－メチルカプトプロパンニトリル、2，7－ジアミノ－4，5－ジチアオクタンニトリル、2－アミノ－4－メチルチオブタンニトリル、2－アミノ－3－フェニルプロパンニトリル、3－（4－ヒドロキシフェニル）プロパンニトリル、2，6－ジアミノヘキサンニトリル、2，6－ジアミノ－5－ヒドロキシヘキサンニトリル、2－アミノ－3－（3－インドリル）プロパンニトリル、2－アミノ－3－（4－イミダゾリル）プロパンニトリル、2－アミノ－2－フェニルエタンニトリル等を例示しうる。

【0008】本発明において原料の光学活性な2－アミノニトリルに、青酸化合物を作用させて2－アミノニトリルラセミ体を生産するには、例えば次の方法を適用するとよい。すなわち、有機溶媒中で青酸化合物と、原料の光学活性な2－アミノニトリルとを接触させて反応さ

せる。上記の反応では種々の有機溶媒を使いうるが、好ましくはメタノール、エタノール、n-プロパノール、イソプロパノール、n-ブタノール等のアルコール類を例示しうる。あるいは、ベンゼン、トルエン、キシレン、ヘキサン、イソオクタン、テトラヒドロフラン、酢酸エチルなどの溶媒と先に述べたアルコール類との混合溶媒などを例示しうる。またその混合比率はどのような割合でもよい。しかし、好ましくは、ベンゼン：メタノールを、85：15v/v の比率で用いるのがよい。青酸化合物としては、シアン化リチウム(LiCN)、シアン化ナトリウム(NaCN)、シアン化カリウム(KCN) などがあげられる。反応は、温度20～50℃の範囲で10分～１時間行なう。上記反応により生成した２－アミノニトリルラセミ体は、相分離、濾過、抽出、カラムクロマトグラフィー等の公知の手段を適用して分離、採取する。

【０００９】次に本発明の実施例を挙げて、本発明を具体的に説明する。

【実施例１】

①溶媒の調製

＊メタノールをモレキュラーシーブにより脱水して溶媒とした。

②ラセミ化

上記の無水メタノール５mlを、直径24mmの試験管に収容し、これにシアン化カリウムKCN ５mgを青酸化合物として光学純度98％eeのＤ－２－アミノ－２－フェニルエタンニトリル50mgと共に加えて密栓し、40℃、300rpmで10分間振盪を行なった。反応終了後、溶媒を留去し、これにベンゼン：ヘキサン（１：１）の溶液を加えて再結晶して、２－アミノ－２－フェニルエタンニトリルの結晶を得た。この結晶をヘキサン：２－プロパノール（９：１）の溶液に溶解し、高速液体クロマトグラフィーで分析した。得られた２－アミノ－２－フェニルエタンニトリルの絶対配置と光学純度の決定にはカラム充填剤として、CHIRALCEL OJ（ダイセル化学工業社製）を用いた。結果は表１に示すとおりである。

【００１０】

【表１】

＊

反応時間(分)	絶対配置	光学純度(％ee)	ラセミ化率(％)
0	D	98	0
10	ラセミ	0	100

【００１１】

【比較例１】

①溶媒の調製

メタノールをモレキュラーシーブにより脱水して溶媒とした。

②ラセミ化

上記の無水メタノール５mlを、直径24mmの試験管に収容し、これに光学純度98％eeのＤ－２－アミノ－２－フェニルエタンニトリル50mgを加えて密栓し、40℃、300rpmで10分間振盪を行なった。反応終了後、溶媒を留去し、※これにベンゼン：ヘキサン（１：１）の溶液を加えて再結晶を行い、２－アミノ－２－フェニルエタンニトリルを得た。これをヘキサン：２－プロパノール（９：１）の溶液に溶解し、高速液体クロマトグラフィーで分析した。得られた２－アミノ－２－フェニルエタンニトリルの絶対配置と光学純度の決定にはカラム充填剤として、CHIRALCEL OJ（ダイセル化学工業社製）を用いた。結果は表２に示すとおりである。

【００１２】

【表２】

反応時間(分)	絶対配置	光学純度(％ee)	ラセミ化率(％)
0	D	98	0
10	D	42	57

【００１３】

【実施例２】

①溶媒の調製

ベンゼンとメタノールを85：15v/v の割合に混合した。

②ラセミ化

上記の混合溶媒５mlを、直径24mmの試験管に収容し、これにシアン化カリウムKCN ５mgを青酸化合物として光学純度98％eeのＤ－２－アミノ－２－フェニルエタンニトリル50mgとともに加えて密栓し、40℃、300rpmで40分間振盪を行なった。反応終了後、有機溶媒相を高速液体クロマトグラフィーで分析した。得られた２－アミノ－２－フェニルエタンニトリルの絶対配置と光学純度の決定にはカラム充填剤として、CHIRALCEL OJ（ダイセル化学工業社製）を用いた。結果は表３に示すとおりである。

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【0014】　　＊　＊【表3】

反応時間(分)	絶対配置	光学純度(%ee)	ラセミ化率(%)
0	D	98	0
10	D	4	96
20	D	4	96
30	D	2	98
40	D	2	98

【0015】
【比較例2】
①溶媒の調製
ベンゼンとメタノールを85：15v/v の割合に混合した。
②ラセミ化
上記の混合溶媒2mlを、直径24mmの試験管に収容し、光学純度98%eeのD－2－アミノ－2－フェニルエタンニトリル5mgを加えて密栓し、40℃、300rpmで6時間振盪※を行なった。反応終了後、有機溶媒相を高速液体クロマトグラフィーで分析した。得られた2－アミノ－2－フェニルエタンニトリルの絶対配置と光学純度の決定にはカラム充填剤として、CHIRALCEL OJ（ダイセル化学工業社製）を用いた。結果は表4に示すとおりである。

【0016】
【表4】

反応時間(分)	絶対配置	光学純度(%ee)	ラセミ化率(%)
0	D	98	0
3	D	96	2
6	D	94	4

【0017】
【実施例3】
①溶媒の調製
ベンゼンとメタノールを85：15v/v の割合に混合した。
②ラセミ化
上記の混合溶媒5mlを、直径24mmの試験管に収容し、これにシアン化カリウムKCN 5mgを青酸化合物として光学純度64%eeのD－2－アミノ－4－メチルペンタンニトリル5μl とともに加えて密栓し、40℃、300rpmで1時間振盪した。
③誘導体化と分析
反応終了後、ただちに2N塩酸を4ml加え撹拌した。塩酸★相を6N水酸化ナトリウムでアルカリ性とし、クロロホルム2mlを加えて撹拌した。クロロホルム相にトリエチルアミン4滴と3，5－ジニトロベンゾイルクロリド5mg加え、60℃で3時間加温した。ヘキサン：メタノール（9：1）混合溶液に誘導体化した2－アミノ－4－メチルペンタンニトリル溶液を3滴加え、高速液体クロマトグラフィーで分析した。得られた2－アミノ－4－メチルペンタンニトリルの絶対配置と光学純度の決定にはカラム充填剤として、CHIRALCEL OJ（ダイセル化学工業社製）を用いた。結果は表5に示すとおりである。

【0018】
【表5】

反応時間(時間)	絶対配置	光学純度(%ee)	ラセミ化率(%)
0	D	64	0
1	D	54	16
3	D	42	34

【0019】
【発明の効果】本発明の方法によると、光学活性2－アミノニトリルに、有機溶媒中で青酸化合物を作用させ、ニトリルを温和な条件でラセミ2－アミノニトリルに変換するので、反応副生成物が少なく、収率よくラセミ体を得ることができる。得られる2－アミノニトリルラセ

7　　8

ミ体は、光学活性なα－アミノ酸類の製造原料として有　　用である。

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// C07D 209/20		9283－4C		
233/64	106			